Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors

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Policy

Single autologous hematopoietic cell transplantation (HCT) may be considered medically necessary as salvage therapy for germ-cell tumors:

- In patients with favorable prognostic factors that have failed a previous course of conventional-dose salvage chemotherapy; or
- In patients with unfavorable prognostic factors as initial treatment of first relapse (i.e., without a course of conventional-dose salvage chemotherapy) and in patients with platinum-refractory disease. (See Policy Guidelines for prognostic factors.)

Tandem or sequential autologous HCT may be considered medically necessary for the treatment of testicular tumors either as salvage therapy or with platinum-refractory disease.

Autologous HCT is considered investigational as a component of first-line treatment for germ-cell tumors.

Allogeneic HCT is considered investigational to treat germ-cell tumors, including, but not limited to use as therapy after a prior failed autologous hematopoietic cell transplantation.

Related Policies

8.01.15  Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
8.01.21  Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms
8.01.22  Allogeneic Hematopoietic Stem-Cell Transplantation for Genetic Diseases and Acquired Anemias
8.01.24  Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
8.01.25  Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases
8.01.29  Hematopoietic Cell Transplantation for Hodgkin Lymphoma
8.01.511 Hematopoietic Cell Transplantation for Solid Tumors of Childhood
Hemopoietic Stem-Cell Transplantation for Non-Hodgkin Lymphomas

Policy Guidelines

The favorable and unfavorable prognostic factors listed next are derived from the current National Comprehensive Cancer Network (NCCN) guidelines and DeVita et al's textbook *Cancer: Principles and Practice of Oncology* (2008, pp. 1463-85).

Patients with favorable prognostic factors include those with a testis or retroperitoneal primary site, a complete response to initial chemotherapy, low levels of serum markers, and low volume disease. Patients with unfavorable prognostic factors are those with an incomplete response to initial therapy or relapsing mediastinal nonseminomatous germ cell tumors.

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Description

Therapy for germ-cell tumors is generally dictated by several factors, including disease stage, tumor histology, site of tumor primary, site of tumor primary and response to chemotherapy. Patients with unfavorable prognostic factors, incomplete initial responses, and early relapse after initial complete response may be candidates for hematopoietic cell transplantation (HCT).

For individuals who have previously untreated germ cell tumors who receive first-line treatment with autologous HCT, the evidence includes randomized controlled trials (RCTs). Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. The available trials found after autologous HCT as initial therapy for germ cell tumors did not significantly improve outcomes compared with alternative therapy (e.g., standard-dose chemotherapy). Study sample sizes were relatively small and may have been underpowered to detect differences between groups. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have relapsed or refractory germ cell tumors who receive autologous HCT, the evidence includes 1 RCT and several case series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. The RCT did not find significant differences in outcomes between autologous HCT plus high-dose chemotherapy and standard-dose chemotherapy. Case series found 3-year overall survival rates that ranged from 55% to 60%; these studies lacked comparison groups. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who germ cell tumors who receive tandem or sequential HCT, the evidence includes 1 RCT,
several retrospective cohort studies, and a comparative effectiveness review. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. The RCT found a higher rate of treatment-related mortality with sequential HCT than with single HCT. However, 5-year survival outcomes did not differ significantly between groups. Overall, the available studies have included heterogeneous patient populations, in different salvage treatment settings (i.e., first vs subsequent salvage therapy), and have lacked a universally accepted prognostic scoring system to risk-stratify patients. Tandem or sequential HCT has not shown benefit in patients with primary mediastinal germ cell tumors. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have germ cell tumors who receive allogeneic HCT, the evidence includes a case report. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. There were no RCTs or non-RCTs evaluating allogeneic HCT for germ cell tumors. One 2007 case report described successful treatment of a refractory mediastinal germ cell tumor with allogeneic HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input obtained in 2010 found strong support for autologous HCT as a treatment of relapsed or refractory germ cell tumors, and for tandem or sequential HCT as salvage therapy for testicular tumors and as treatment of platinum-refractory testicular tumors. The clinical input is generally consistent with recommendations in national and international guidelines. Thus, these indications may be considered medically necessary.

BackgroundHematopoietic Cell Transplantation

HCT refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole body radiation therapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naive” and thus are associated with a lower incidence of rejection or graft versus host disease. Cord blood is discussed in greater detail in a separate medical policy. (See Related Policies)

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II loci on chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

Germ-Cell Tumors

Germ-cell tumors are composed primarily of testicular neoplasms (seminomas or nonseminomatous tumors) but also include ovarian and extragonadal germ-cell tumors (e.g., retroperitoneal or mediastinal tumors). Germ-cell tumors are classified according to their histology, stage, prognosis, and response to chemotherapy.

Germ cell tumor histologies include seminoma, embryonal carcinoma, teratoma, choriocarcinoma, yolk sac tumor, and mixed germ-cell tumors. Seminomas are the most common; all other types are collectively referred to as nonseminomatous germ-cell tumors.

Stage is dependent on location and extent of the tumor, using the American Joint Committee on Cancer’s TNM system. TNM stages, modified by serum concentrations of markers (S0-3) when available, are grouped by similar prognoses. Markers used for germ-cell tumors include human beta-chorionic gonadotropin (B-hCG), lactate dehydrogenase (LDH), and alpha fetoprotein (AFP). Pure seminoma does not have elevated AFP levels except for very rare cases with very minimal elevations whereas B-hCG may be elevated in about 20% of seminomas, especially if there is a large tumor burden. Elevations of AFP indicate a non-seminomatous component present. For testicular tumors, Stages IA-B have tumors limited to the testis (no involved nodes or distant metastases) and no marker elevations (S0); Stages IIA-C have increasing size and number of tumor-involved lymph nodes, and at least one marker moderately elevated above the normal range (S1); Stages IIIA-C have distant metastases and/or marker elevations greater than specified thresholds (S2-3).

Germ-cell tumors also are divided into good-, intermediate-, or poor-risk categories based on histology, site,
extent of primary tumor, and serum marker levels. Good-risk pure seminomas can be at any primary site, lack marker elevations, and lack nonpulmonary visceral metastases. Intermediate-risk pure seminomas have nonpulmonary visceral metastases with or without elevated hCG and/or LDH. There are no poor-risk pure seminomas. Mixed histology tumors and seminomas with elevated AFP (due to mixture with nonseminomatous components) are managed as nonseminomatous germ-cell tumors. Good- and intermediate-risk nonseminomatous germ-cell tumors have testicular or retroperitoneal tumors without nonpulmonary visceral metastases, and either S1 (good risk) or S2 (intermediate) levels of marker elevations. Poor-risk tumors have mediastinal primary tumors, or nonpulmonary visceral metastases, or the highest level (S3) of marker elevations.

Therapy for germ-cell tumors is generally dictated by stage, risk subgroup, and tumor histology. Testicular cancer is divided into seminomatous and nonseminomatous types for treatment planning because seminomas are more sensitive to radiation therapy. Stage I testicular seminomas may be treated by orchiectomy with or without radiation or single-dose carboplatin adjuvant therapy. Nonseminomatous stage I testicular tumors may be treated with orchiectomy with or without retroperitoneal lymph node dissection. Higher stage disease typically involves treatment that incorporates chemotherapy. First-line chemotherapy for good- and intermediate-risk patients with higher-stage disease is usually 3 or 4 cycles of a regimen combining cisplatin and etoposide, with or without bleomycin depending on histology and risk group. Chemotherapy is often followed by surgery to remove residual masses. Second-line therapy often consists of combined therapy with ifosfamide/mesna and cisplatin, plus vinblastine, paclitaxel, or etoposide (if not used for first-line treatment). Patients whose tumors are resistant to cisplatin may receive carboplatin-containing regimens. The probability of long-term continuous complete remission diminishes with each successive relapse.

Regulatory Status
The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation (CFR) title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Scope
Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

Benefit Application
The following considerations may supersede this policy:
- State mandates requiring coverage for autologous bone marrow transplantation offered as part of National Institutes of Health–approved clinical trials of autologous bone marrow transplantation.
- Some plans may participate in voluntary programs offering coverage for patients participating in National Institutes of Health–approved clinical trials of cancer chemotherapies, including autologous bone marrow transplantation.

Some contracts or certificates of coverage (e.g., FEP) may include specific conditions in which autologous bone marrow transplantation would be considered eligible for coverage.

Rationale
Autologous Hematopoietic Stem-Cell Transplantation as first line Therapy of Germ-Cell Tumors

Daugaard et al. (2011) reported the outcomes of a randomized Phase III study comparing standard-dose cisplatin, etoposide, and bleomycin (BEP) to sequential high-dose cisplatin, etoposide, and ifosfamide (VIP) plus stem-cell support in previously untreated males with poor-prognosis germ-cell cancer. The study aimed to recruit 222 patients but closed with 137 patients from 27 European oncology centers due to slow accrual. Patients were age 15 to 50 years and had previously untreated metastatic poor-prognosis nonseminomatous germ-cell tumor of either testicular or extragonadal origin. Median follow-up was 4.4 years. Toxicity was more severe in the patients who received high-dose chemotherapy (HDC), and toxic death was reported in 2 patients who received HDC and one in the BEP arm. There was no improvement in complete response (CR) rate in the HDC arm versus the standard-dose arm (44.6% vs. 33.3%, respectively, p=0.18). There was no difference in failure-free survival (FFS) between the two groups. At 2 years, FFS was 44.8% (95% confidence interval [CI], 32.5 to 56.4) and 58.2% (95% CI: 48.0-71.9), respectively, for the standard- and high-dose arms. The difference was not statistically significant (p=0.06). OS did not differ between the two groups (log-rank p>0.1). The authors concluded that HDC given as part of first-line therapy does not improve outcomes in patients with poor-prognosis germ-cell tumor.

Motzer et al. (2007) reported on a Phase III prospective, randomized, multicenter trial of 219 previously untreated patients with poor-prognosis germ-cell tumors. The median patient age was 28 years. Patients were randomized to receive either conventional chemotherapy (four cycles of BEP) (n=111), or 2 cycles of BEP followed by two cycles of HDC with autologous HCT. Median follow-up was 51 months. One-year durable CR rate was 52% after BEP and HDC with HCT, and 48% after BEP alone (p=0.53). There was no survival difference at 106 months for patients treated with HDC and HCT (68%) compared with patients treated with conventional chemotherapy (69%).

Droz et al. (2007) assessed the impact of HDC plus HCT on the survival of patients with high-volume, previously untreated, metastatic nonseminomatous germ-cell tumors. Patients were randomized to four cycles every 21 days of vinblastine, etoposide, cisplatin and bleomycin (n=57) or a slightly modified regimen followed by HDC and autologous HCT (n=57). In an intention-to-treat (ITT) analysis, there were 56% and 42% CRs in the conventional and HDC groups, respectively (p=0.099). Median follow-up was 9.7 years, and no significant difference between OS was observed (p=0.167).

Section Summary

The evidence from several randomized trials found that autologous HCT as initial therapy for germ cell tumors did not significantly improve outcomes compared with alternative therapy (e.g., standard-dose chemotherapy). However, study sample sizes were relatively small and may have been underpowered to detect differences between groups.

Autologous HCT for Relapsed or Refractory Germ-cell Tumors

The evidence related to the use of autologous HCT for relapsed or treatment-refractory germ-cell tumors consists of 1 randomized controlled trial (RCT) and several nonrandomized observational studies.

In 2005, Pico et al. reported on a randomized trial comparing four cycles of conventional-dose chemotherapy with three cycles of the same regimen followed by carboplatin-based HDC plus autologous HCT in 280 patients who had relapsed after a complete or partial remission following first-line therapy with a cisplatin-based regimen. The authors reported no significant differences between treatment arms in three-year EFS and OS. However, the study began before international consensus established the current risk group definitions; thus, Pico et al. likely included some patients now considered to have good prognosis at relapse. Furthermore, while 77% and 86% of patients in the control and experimental arms, respectively, had at least one elevated serum tumor marker, they did not report how highly elevated these were and did not compare arms with respect to the marker thresholds that presently determine risk level (S1-3). Finally, HDC in the experimental arm followed three cycles of conventional-dose chemotherapy, which differs from most current practice in the U.S., in which a single cycle is...
used before HDC. As a consequence, 38 of 135 (28%) randomized to the HDC arm did not receive HDC because of progression, toxicity, or withdrawal of consent.

Seftel et al. (2011) conducted a multicenter cohort study of consecutive patients undergoing a single autologous HCT for germ-cell tumor between January 1986 and December 2004. Of 71 subjects, median follow-up was 10.1 years. The median age was 31 years (range 16–58 years). A total of 67 of the patients had nonseminomatous germ-cell tumors and 4 had seminomatous germ-cell tumors. A total of 57 patients had primary gonadal disease and 14 had primary extragonadal disease. Of the latter, 11 patients presented with primary mediastinal disease, 2 presented with primary central nervous system (CNS) disease, and 1 presented with retroperitoneal disease. In all, 28 patients underwent autologous HCT for relapsed disease after achieving an initial CR. Of these, 24 patients underwent autologous HCT after a first relapse, whereas 4 patients underwent transplant after a second relapse. An additional 36 patients achieved only an incomplete response after initial therapy and proceeded to autologous HCT after salvage chemotherapy for active residual disease. OS at 5 years was 44.7% (95% CI: 32% to 56.5%) and EFS, 43.5% (95% CI: 31.4% to 55.1%). There were 7 (10%) treatment-related deaths within 100 days of transplant. Three (4.2%) patients developed secondary malignancies. Of 33 relapses, 31 occurred within 2 years of the transplant. Two very late relapses occurred 13 and 11 years after transplant. In a multivariate analysis, a favorable outcome was associated with International Germ Cell Consensus Classification (IGCCC) good prognosis disease at diagnosis, primary gonadal disease, and response to salvage chemotherapy.

Agarwal et al. (2009) reported their experience at Stanford in treating 37 consecutive patients who received HDC and autologous HCT between 1995 and 2005 for relapsed germ-cell tumors. The median patient age was 28 years (range, 9-59 years), with 34 males and three females. Primary tumor sites included 24 testes/adnexal, 10 chest/neck/retroperitoneal, and 3 CNS. Twenty-nine of the patients had received prior standard salvage chemotherapy. Three-year OS was 57% (95% CI: 41% to 71%), and 3-year PFS was 49% (95% CI: 33% to 64%).

Baek et al. (2013) reported results of a small feasibility study of HDC followed by HCT for patients with relapsed or progressed CNS germ-cell tumors. The authors enrolled 11 patients with nongerminomatous (i.e., nonseminomatous) germ-cell tumors and nine patients with germinomatous stem-cell tumors, all of whom had received conventional chemotherapy with or without radiation before HCT. Sixteen patients received an initial course of HDC with carboplatin, thiopental, and etoposide followed by HCT, and nine of those received a second course of HDC with cyclophosphamide-melphalan followed by a second HCT (see “Tandem and Sequential HCT for Germ-Cell Tumors,” next). Twelve patients remained alive at a median follow-up of 47 months (range, 22-90 months), with a probability of 3-year OS of 59.1%.

In 2015, Nieto et al reported on 43 male patients with poor-risk relapsed or refractory germ cell tumors with received HDC and autologous HCT. Primary tumors were testicular in 32 patients, mediastinal in 7 patients, and retroperitoneal in 4 patients. Median follow-up was 46 months (range, 9-84 months). At follow-up, the relapse-free survival rate was 55.8% and the OS rate was 58.1%. Relapse-free survival rates were 66% in patients with testicular primaries, 28.5% in patients with mediastinal primaries and 25% in patients with retroperitoneal primaries.

**Section Summary**
The single published RCT did not find improved outcomes with HDC and autologous HCT than with standard-dose HCT. Case series had sample sizes ranging between 11 and 71 patients each. Three-year OS rates in the case series ranged between 55% and 60%.

**Tandem and Sequential HCT for Germ-Cell Tumors**
There is ongoing research into the role of tandem and sequential HCT for germ-cell tumors, with a variety of specific chemotherapy regimens.

Lorch et al. (2007) compared single- versus sequential HDC with autologous HCT as first or subsequent salvage treatment in patients with relapsed or refractory germ-cell tumors. Patients were randomized to 2 different HDC regimens (arm A, arm B). Most tumors were gonadal primaries; 10% of patients in arm A had retroperitoneal, mediastinal, or CNS primaries, and 11% of patients in arm B had retroperitoneal or mediastinal primaries. This represented the first salvage therapy received for 86% of the patients in arm A and 85% in arm B, whereas 14% in arm A and 15% in arm B had received 1 or more previous salvage regimens before...
randomization. A total of 111 (51%) of 216 patients were randomized to sequential high-dose therapy, and 105 (47%) of 216 patients were randomized to single high-dose therapy. The trial was stopped prematurely after recruitment of 216 patients as a result of excess treatment-related mortality in arm B (sequential). There was a planned interim analysis after the inclusion of 50% of the required total number of patients. Survival analyses were performed on an ITT basis.

With a median follow-up time of 36 months, 109 (52%) of 211 patients were alive, and 91 (43%) of 211 patients were progression-free. At one year, EFS, PFS, and OS rates were 40%, 53%, and 80%, respectively, in arm A compared with 37%, 49%, and 61%, respectively, in arm B (p >0.05 for all comparisons). Survival rates were not reported separately by primary site of the tumor. No difference in survival probabilities was found between the single and sequential high-dose regimens; however, sequential high-dose therapy was better tolerated and resulted in fewer treatment-related deaths. Treatment-related deaths, mainly as a result of sepsis and cardiac toxicity, were less frequent in arm A (4/108 patients, 4%) compared with arm B (16/103 patients, 16%; p <0.01). The authors state that the higher treatment-related deaths observed in arm B likely were due to the higher dosages per HCT cycle in the arm B regimen compared with arm A, and the toxic renal and cardiac effects of cyclophosphamide used in arm B. The authors attributed the higher rate of treatment-related deaths in arm B to the higher dosages per HCT cycle in the arm B regimen compared with arm A, as well as the toxic renal and cardiac effects of cyclophosphamide used in arm B.

Lorch et al (2012) reported long-term results from this study reported 5-year PFS as 47% (95% CI: 37% to 56%) in arm A and 45% (95% CI: 35% to 55%) in arm B (hazard ratio [HR], 1.16; 95% CI: 0.79 to 1.70; p=.454). Five-year OS was 49% (95% CI: 40% to 59%) in arm A and 39% (95% CI: 30% to 49%) in arm B (HR=1.42; 95% CI: 0.99 to 2.05; p=.057). The authors concluded that patients with relapsed or refractory germ-cell tumors can achieve durable long-term survival after single, as well as sequential HCT and that fewer early deaths related to toxicity translated into superior long-term OS after sequential HCT.

Lazarus et al. (2007) reported the results of autologous HCT in relapsed testicular/germ-cell cancer from registry data from the Center for International Blood and Marrow Transplant Research.(12) Patients with mediastinal primaries were excluded. Data included 300 patients from 76 transplant centers in 8 countries who received either a single transplant or tandem autologous HCT between 1989 and 2001. Of the 300 patients, 102 received tandem, and 198 single planned autologous HCT. PFS and OS at 1, 3, and 5 years was similar for both groups. The probability of PFS at 5 years for the tandem transplant group was 34% (95% CI: 25% to 44%) versus 38% (95% CI: 31% to 45%) in the single transplant group; p=0.50. The probability of 5-year OS was 35% (95% CI: 25% to 46%) versus 42% (95% CI: 35 to 49%), respectively (p=0.29).

Lotz et al. (2005) reported the results of a Phase II study on three consecutive cycles of HDC regimens supported by autologous HCT in 45 poor-prognosis patients with relapsed germ-cell tumors.(13) From March 1998 to September 2001 (median follow-up, 31.8 months), 45 patients (median age, 28 years) were enrolled. Most of the patients (76%) had testicular primaries; 13% had mediastinal primaries; 11% retroperitoneal, hepatic, or unknown. Of all patients, 22 received the complete course. Twenty-five patients died from progression and five from toxicity. The overall response rate was 37.7%, including an 8.9% CR rate. The median OS was 11.8 months. The three-year survival and PFS rate was 26%. The authors used the “Beyer” prognostic score to predict the outcome of HDC and concluded that patients with a Beyer score greater than two did not benefit from this approach, confirming that highly refractory patients and particularly patients with resistant/refractory primary mediastinal germ-cell tumors do not benefit from HDC. The authors also state that better selection criteria have to be fulfilled in forthcoming studies.

Einhorn et al. (2007) reported retrospectively on a series of 184 patients, treated between 1996 and 2004, with two consecutive cycles of HDC for metastatic testicular cancer that had progressed (relapsed) after receiving cisplatin-containing combination chemotherapy.(14) Patients with primary mediastinal nonseminomatous germ-cell tumors or tumors with late relapse (2 or greater years after previous therapy) were excluded. The patient population included those with initial IGCCC stage defined as low risk (39%), intermediate risk (21%), and high risk (41%) and both platinum-sensitive and refractory disease at the beginning of HDC. Results from this experienced center showed that of the 184 patients, 116 had complete remission of disease without relapse during a median follow-up of 48 months. Of the 135 patients who received the treatment as second-line therapy (i.e., first salvage setting), 94 (70%) were disease-free during follow-up; 22 (45%) of 49 patients who received treatment as third-line or later therapy were disease-free. Of 40 patients with cancer that was refractory to standard-dose platinum, 18 (45%) were disease-free.

Letters to the editor regarding the Einhorn et al. study noted the lack of a validation set for the prognostic scoring
In response to requests, input was received from 3 physician specialty societies, 3 academic medical centers, and unless otherwise noted. Recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In a subsequent study from the same center as the Einhorn et al. study, Suleiman et al. (2013) evaluated the outcomes for 12 patients with recurrent primary mediastinal nonseminomatous germ-cell tumors after initial treatment with cisplatin-containing combination chemotherapy, a population excluded from their previous study, who were treated with tandem HCT.(15) Patients received 2 consecutive courses of HDC (carboplatin and etoposide) followed by HCT. Overall outcomes were poor, with a median survival of 11 months (range, 4-52 months), but 3 of 12 patients achieved a complete remission. One patient remained free of disease at 50 months of follow up, and 1 remained free of disease after tandem HCT and subsequent mediastinal surgery at 52 months of follow-up.

Pal et al. (2013) reported 5-year follow up results from a retrospective case series of 48 patients with relapsed germ-cell tumors who were enrolled in a study to evaluate the effectiveness of 2 sequential cycles of HDC (paclitaxel, etoposide, and carboplatin in the first cycle, followed by dose of high-dose paclitaxel, ifosfamide, and carboplatin) followed by HCT.(16) Forty-three patients (91.5%) had nonseminomatous histology. Most patients (n=39) had received two prior chemotherapy regimens; 6 patients had received 3 prior regimens. Thirty-four patients had intermediate risk classification by the Beyer score and the remainder had high risk classification. Of the 48 patients enrolled, 17 received only one course of HDC, 11 due to progressive disease, five due to toxicities, and 1 due to a severe fungal infection. A total of 17 patients of the 48 enrolled were alive and progression-free at a median of 123.2 months (range, 51.6-170.2 months); 25 died, most (n=23) due to disease progression. Of the 23 patients who were alive after receiving per-protocol therapy, 18 were contacted for interviews at a median 115.6 months (range, 38.9-185.9 months) post-enrollment and underwent a cancer-related quality-of-life assessment with the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire—Core 30 (QLQ-C30). The overall average score on the questionnaire was 87.04 (SD=14.64); the authors compared quality-of-life scores in this cohort to a separate cohort of 150 patients with germ-cell tumors who received chemotherapy, and reported that patients in their cohort had significantly higher global health scores (87.04 vs. 75.62, p=0.02), but lower physical functioning scores (68.9 vs. 92.7, p<0.001). The authors conclude that tandem HDC followed by HCT is a reasonable option for relapsed germ-cell tumors, with long-term survivors demonstrating a reasonable quality of life.

A 2012 comparative effectiveness review conducted for the Agency for Healthcare Research and Quality on the use of HCT in the pediatric population concluded that, for germ-cell tumors, the body of evidence on OS with tandem HCT compared with single HCT for the treatment of relapsed pediatric germ-cell tumors was insufficient to draw conclusions.(17)

**Section Summary**

One RCT compared tandem and sequential HCT for germ cell tumors. This RCT showed higher treatment-related mortality with sequential HCT than with single HCT. Five-year survival outcomes, however, did not show significant differences between groups. Observational studies have included heterogeneous patient populations, in different salvage treatment settings (i.e., first vs subsequent salvage therapy), and lacked a universally accepted prognostic scoring system to risk-stratify patients.

**Allogeneic HCT for Germ-cell Tumors**

No RCTs or non-RCTs evaluating allogeneic HCT for germ cell tumors were identified. One 2007 case report described successful treatment of a refractory mediastinal germ cell tumor with allogeneic HCT.(18)

**Clinical Input Received Through Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 3 physician specialty societies, 3 academic medical centers, and
5 Blue Distinction Centers for Transplants while this policy was under review in 2010. There was general agreement with the policy statements regarding the use of single autologous hematopoietic cell transplantation (HCT) as salvage therapy, the use of autologous HCT as first-line treatment, and the use of allogeneic HCT. Seven reviewers felt that tandem or sequential HCT is medically necessary for patients as salvage therapy or with platinum-refractory disease; 2 reviewers felt that tandem or sequential HCT was investigational.

Summary Of Evidence
For individuals who have previously untreated germ cell tumors who receive first-line treatment with autologous hematopoietic cell transplantation (HCT), the evidence includes randomized controlled trials (RCTs). Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. The available trials found after autologous HCT as initial therapy for germ cell tumors did not significantly improve outcomes compared with alternative therapy (e.g., standard-dose chemotherapy). Study sample sizes were relatively small and may have been underpowered to detect differences between groups. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have relapsed or refractory germ cell tumors who receive autologous HCT, the evidence includes 1 RCT and several case series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. The RCT did not find significant differences in outcomes between autologous HCT plus high-dose chemotherapy and standard-dose chemotherapy. Case series found 3-year overall survival rates that ranged from 55% to 60%; these studies lacked comparison groups. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who germ cell tumors who receive tandem or sequential HCT, the evidence includes 1 RCT, several retrospective cohort studies, and a comparative effectiveness review. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. The RCT found a higher rate of treatment-related mortality with sequential HCT than with single HCT. However, 5-year survival outcomes did not differ significantly between groups. Overall, the available studies have included heterogeneous patient populations, in different salvage treatment settings (i.e., first vs subsequent salvage therapy), and have lacked a universally accepted prognostic scoring system to risk-stratify patients. Tandem or sequential HCT has not shown benefit in patients with primary mediastinal germ cell tumors. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have germ cell tumors who receive allogeneic HCT, the evidence includes a case report. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. There were no RCTs or non-RCTs evaluating allogeneic HCT for germ cell tumors. One 2007 case report described successful treatment of a refractory mediastinal gem cell tumor with allogeneic HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this policy are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00432094</td>
<td>Autologous Peripheral Blood Stem Cell Transplant for Germ-Cell Tumors</td>
<td>25</td>
<td>Jan 2017</td>
</tr>
<tr>
<td>NCT00936936</td>
<td>High-dose Chemotherapy for Poor-prognosis Relapsed Germ-cell Tumors</td>
<td>68</td>
<td>Jun 2018</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN) Guidelines
Current National Comprehensive Cancer Network guidelines on testicular cancer (v.1.2017) state that, for patients with unfavorable prognostic features (e.g., incomplete response to first-line treatment), high-dose
chemotherapy followed by autologous hematopoietic cell transplant (HCT) is a treatment option. The guidelines do not address the use of tandem or sequential HCT in the treatment of testicular tumors.

**American Society for Blood and Marrow Transplantation**

In 2015, guidelines by the American Society for Blood and Marrow Transplantation were published on indications for autologous and allogeneic HCT. Recommendations were intended to describe the current consensus on use of HCT within and outside of the clinical trial setting. Recommendations on germ cell tumors are listed in Table 2.

**Table 2. ASBMT Recommendations on Allogeneic and Autologous HCT**

<table>
<thead>
<tr>
<th>Indications</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pediatric</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germ cell tumor, relapse</td>
<td>D</td>
<td>C</td>
</tr>
<tr>
<td>Germ cell tumor, refractory</td>
<td>D</td>
<td>C</td>
</tr>
<tr>
<td><strong>Adult</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germ cell tumor, relapse</td>
<td>N</td>
<td>C</td>
</tr>
<tr>
<td>Germ cell tumor, refractory</td>
<td>N</td>
<td>C</td>
</tr>
</tbody>
</table>

ASBMT: American Society for Blood and Marrow Transplantation; C: clinical evidence available, standard of care; D: developmental (ie promising); HCT: hematopoietic cell transplantation N: not generally recommended.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**References**


Appendix

N/A

History

<table>
<thead>
<tr>
<th>Date</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/09/14</td>
<td>New PR policy replacing 8.01.35, added to Therapy section. Policy developed with literature review through March 5, 2014. Policy statement on tandem or sequential autologous HSCT as medically necessary for the treatment of testicular tumors germ cell tumors either as salvage therapy or with platinum-refractory disease now requires enrollment in a clinical trial.</td>
</tr>
<tr>
<td>02/03/15</td>
<td>Update Related Policies. Remove 8.01.23, 8.01.28 and 8.01.30.</td>
</tr>
</tbody>
</table>
06/09/15  Annual Review. Policy updated with literature review; no change in policy statements. ICD-9 and ICD-10 diagnosis and procedure codes removed; these were for informational purposes only.
09/01/16  Update Related Policies. Remove 8.01.27 as it was archived.
11/01/16  Annual Review, approved October 11, 2016. Policy updated with literature review through June 14, 2016; references 2, 17, 38, and 46 added. Policy statements unchanged. Removed codes that are transplant benefit related. Codes listed in the policy will be reviewed for medical necessity.
04/01/17  Annual Review, approved March 14, 2017. Policy updated with literature review through November 9, 2016; references 9 and 20 added. Changed “hematopoietic stem cell transplantation” to “hematopoietic cell transplantation” per NCCN terminology change. Policy statements unchanged.
06/09/17  Coding update; updated description for CPT codes 38230, 38240, and 38241.
08/01/17  Updated title of Related Policy 8.01.511.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA).
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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at

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